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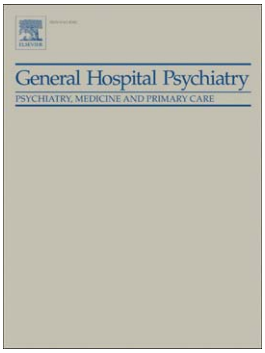
DOI:
10.1016/j.genhosppsych.2014.05.016



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PII: S0163-8343(14)00150-9
DOI: doi: 10.1016/j.genhosppsych.2014.05.016
Reference: GHP 6868

To appear in: *General Hospital Psychiatry*

Received date: 22 August 2013
Revised date: 22 May 2014
Accepted date: 26 May 2014

Please cite this article as: Rodrigues José Daniel Machado, Santos Lapa Maria Georgina, Brockington Ian Fraser, Psychotic episode secondary to gonadotrophins, *General Hospital Psychiatry* (2014), doi: 10.1016/j.genhosppsych.2014.05.016

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Key words:

Estrogen; estradiol; gonadotrophins; in vitro; psychotic.

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Abstract

Objective: To report a case of a substance-induced psychotic disorder secondary to ovulation induction therapy with gonadotrophins.

Method: Case report.

Results: We report a case of a psychotic episode secondary to gonadotrophins therapy. The acute episode was treated with antipsychotic (Aripiprazole). After two years the patient remains free of psychotic symptoms.

Conclusion: There have been several reports correlating low levels of estrogen with psychotic symptoms, leading to studies evaluating the possible effect of this hormone as an antipsychotic. In this case, we report psychotic symptoms with high levels of estradiol, which is contrary to that theory.

1. Introduction

Psychotic symptoms are common manifestations of a wide range of diseases, hence the mandatory exclusion of association with the direct physiological effects of a substance or another medical condition for most psychiatric diagnosis (1). Estrogen has been associated with a potential protective factor for psychosis in women. Evidence comes from studies on gender differences, investigation on estradiol levels and case reports (2)(3)(4)(5). We present a case of substance-induced psychotic disorder secondary to ovulation induction therapy with gonadotrophins. There have been several articles on psychological distress related to infertility treatments published. The most common psychological symptoms are anger, guilt, marital distress, lowered self-esteem, sexual dysfunction, social isolation, irritability, mood swings, feeling down, and bloating (6)(7). Psychotic symptoms are rare and to the best of our knowledge there is no reports of a similar case.

2. Case Report

Mrs. F. is a 40-year-old married woman, with uterine pathology that caused secondary infertility. She tried five times to conceive using *in vitro* fertilization. On the last two attempts she used a combination of follitropin alfa and human menopausal gonadotrophin. Follitropin alfa is a preparation of recombinant human follicle-stimulating hormone (rhFSH), which stimulates ovarian follicular growth in women who do not have primary ovarian failure. Human menopausal gonadotrophin (HMG) is a combination of luteinizing hormone (LH) and follicle-stimulating hormone (FSH); it has a central role in ovulation induction. During her fourth ovarian stimulation, in May 2011, she suffered from headache and an unusual feeling that something was different with her. These feelings faded away in a few days without any medical intervention, and with no social impact. The infertility treatment was unsuccessful. In September 2011 she underwent her fifth ovarian stimulation, again with rhFSH and HMG. On the second day she developed auditory hallucinations ("I heard a man, a women and a child… they insulted me… they told me I was worthless") and persecutory delusions ("I thought the neighbours were stealing electric power and cable television from us"), with periods of psychomotor agitation. She became functionally disturbed and was admitted to a private accident & emergency department, where she was prescribed Aripiprazole 15 mg per day after a clinical observation by an experienced psychiatrist, and a second psychiatric appointment was scheduled. After a few weeks, due to her unshakeable belief that the neighbors were stealing from them, the couple felt forced to move to another abode. She was then referred by her family doctor to a public hospital, where she was observed at triage. She had no psychotic symptoms, but was experiencing weakness, fatigue and loss of energy. She reported no personal or family history of psychiatric problems and denied any illicit

drug intake. Aripiprazole was reduced to 10mg per day while further investigation and family counseling were undertaken. Due to her uterine pathology, she suffered from menorrhagia and anaemia. Blood transfusions were prescribed and it was decided to proceed to hysterectomy. After discharge from Surgery, she had no complains except for regret that she didn't consult a psychiatrist sooner ("that way maybe I would not have had to move house"). She had full insight to the psychotic episode, and felt sad because she did not like the new house. At April 2012 it was decided to stop Aripiprazole. After one month she was asymptomatic (May 2012). We kept her on periodic medical supervision. She remained asymptomatic until November 2013. At this point, her grandfather passed away and she was under uncommon pressure at work. She anticipated the appointment and presented with anxiety symptoms associated with a terrible fear of becoming psychotic again. There was no evidence of positive psychotic symptoms. She was prescribed Clonazepam 0,5mg twice a day. After three weeks her anxiety was improved but she was not completely asymptomatic. She was prescribed Sertraline 25mg and discontinued Clonazepam (December 2013). After a few weeks she became asymptomatic, and by May 2014 she remained asymptomatic, with just treatment with Sertraline 25mg per day. We believe that this second episode has no relation to her previous psychotic one. Symptoms and circumstances were different. She gave informed consent for the publication of his case.

3. Discussion

Several reports associate low estrogen levels with psychotic symptoms and its possible effect as an antipsychotic has been studied with no consistent results (8) (9). Against this, Choi *et al*. (2001) found no statistically significant relation between serum levels of estradiol and worsening of the symptoms in female schizophrenic inpatients (10). Those findings suggest that premenstrual exacerbation of symptoms in female patients may not be a worsening of the schizophrenic symptoms but a concurrence of affective, behavioral, and somatic symptoms. But the influence of estrogen on psychotic symptoms was noticed a long time ago by well known psychiatrists such as Krafft-Ebing, Kretschmer and Kraepelin (1909) (11). There is evidence that low estrogen levels are related to psychotic symptoms (12) (13) (5). In the present case, although no estrogens levels were available, but we can assume that they were high due to the ovarian stimulation pharmacotherapy.

This is not the first case reporting psychotic episode or exacerbation of psychotic symptoms with high levels of estrogen. Siedentopf *et al*. reported a psychotic reaction to Clomiphene citrate, and they cited three similar cases (14); there was no reference to estradiol levels, but they were probably high secondary to Clomiphene citrate therapy, as that is a described effect of this substance (15). Our case is also contrary to the theory that estrogens acts on the brain as an antipsychotic (16). As in our case, Constant reported two cases where gonadotrophin hormone was associated with psychotic symptoms (17).It is still unknown how low estrogen levels produce psychotic symptoms. It may not be a direct correlation. We posited that in our case, the high estrogens levels might have enhanced dopamine activity. We can find in the literature some investigations suggesting the same (18)(19).Other authors agree and suggest that estrogen may provide a state of "decreased vulnerability" through changes in neurotransmitter systems without direct action on basic

pathophysiological mechanisms (20). We found no evidence in medical history, physical examination or auxiliary tests of another plausible cause for the psychotic symptoms. Supporting our hypothesis that *in vitro* fertilization was the cause, is the fact that the patient reported similar, although attenuated, symptoms after a previous treatment with the same substances.

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